Pathogenesis of an Unexpected Sudden Death: Role of Early Cycle Ventricular Premature Contractions

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A 61 year old man who had been studied extensively died unexpectedly ("instantaneously") outside the hospital while wearing an electrocardiographic recorder. Death was caused by ventricular fibrillation, which was initiated by an early cycle ventricular premature contraction occurring in the vulnerable period of repolarization. Such early cycle ventricular premature contractions had been noted in recordings 4 years previously but had never been observed to encroach on the T wave until 5 minutes before death. In the intervening period, the patient had shown increasing evidence of myocardial ischemia and hypertrophy and congestive heart failure, which had been partly obscured by his concealment or denial of symptoms and refusal to change his pattern of activities. Autopsy revealed two old myocardial infarcts and pronounced left ventricular hypertrophy. There was advanced occlusive arteriosclerosis of the major coronary vessels with a recent thrombus in the right coronary artery.

Most unexpected sudden deaths that occur outside the hospital are caused by the abrupt development of fatal cardiac arrhythmias. Autopsy studies[1–4] and studies of people who have been resuscitated[5–8] indicate that about one third of these fatal arrhythmias occur in the setting of an acute myocardial infarction and that most of the remaining two thirds occur in hearts with extensive coronary atherosclerosis and myocardial scarring. However, it is not known why these arrhythmias occur when they do or what initiates them.

In a 10 year prospective study of a random sample of 371 men, we found that those who died suddenly of arrhythmia had both severe myocardial disease (acute infarction, ischemia, hypertrophy, dilatation, congestive heart failure or cardiomyopathy) plus a serious disorder of the cardiac conduction system (dysrhythmia, abnormalities of the sinus node, conduction delays or abnormal patterns of atrioventricular (A-V) or QRS conduction).[9] To extend and amplify these observations, we began in 1973 to investigate the immediate precursors of sudden death by performing frequent prospective observations of 441 actively employed men aged 40 to 65 years. The study group included 332 men selected from medical records as having many risk factors for sudden death. The selection of this sample has been described elsewhere.[10]

On March 4, 1975 one of these men died unexpectedly a few hours after his last examination while he was wearing an electrocardiographic recorder. The terminal event and the events preceding it were observed in detail, and a complete electrocardiographic recording was obtained. The data from these, and the serial observations of this subject over a period of 4 years, yielded detailed information bearing on the pathogenesis of unexpected sudden death.

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Case Report

Medical History

The subject was a 61 year old manager in a large international company with offices in midtown New York. He was selected for participation in this study as a "high risk" man who had had two previous myocardial infarctions and continued to have angina pectoris. He had been healthy and active throughout his childhood and youth. At age 22 years at a preemployment examination, his blood pressure was 146/80 mm Hg. At subsequent examinations, it ranged from 130 to 146/80 to 86 mm Hg. He had no major disabling illnesses until he had his first myocardial infarct in 1956 at age 42 years. At that time he was described as a man who had been "working too hard, smoking two or three packs of cigarettes per day, drinking and eating too much, and having too little sleep." He was 172 cm tall, weighed 91.8 kg and was described as "obese." The hospital report of the illness describes a clinical course and electrocardiographic tracings consistent with an acute diaphragmatic myocardial infarction. He recovered without complication and returned to work after 11 weeks. While he was in the hospital, he stopped smoking.

During the next 13 years, he was active and without cardiovascular symptoms except for several brief episodes of chest pain on exertion. During the 4 years after his myocardial infarction, his blood pressure was recorded at 154 to 158/100 to 102 mm Hg; thereafter it was consistently reported to be 130/80 mm Hg. Chest roentgenograms in 1960 and again in 1966 were reported to show a cardiac contour with "left ventricular prominence" but "no enlargement." The first electrocardiographic evidence suggesting left ventricular hypertrophy appeared in 1969 when he was 55 years old.

A second myocardial infarct occurred in 1969. It was manifested by typical symptoms, signs and clinical course and by an electrocardiogram showing acute S-T elevations in leads II, III and aVF, with a subsequent evolution of the tracings consistent with an acute diaphragmatic myocardial infarct. Twenty-four hours after the onset of this acute illness, a standard electrocardiogram recorded five complexes of an idioventricular rhythm at a rate of 100 to 110/min with coupling intervals ranging from 480 to 600 msec and a configuration like that of the ventricular premature contractions found in later recordings. After recovery, he complained of episodes of chest pain characteristic of typical angina pectoris. The episodes occurred about once a day. He did not use nitroglycerin but waited for the pain to subside spontaneously.

Findings at Initial Examination

On entry into the study in 1971 at age 57, the subject was described as "an unusually robust man" and "an intense and driving individual." He weighed 83.7 kg. A thrusting and diffuse cardiac apical impulse was located in the midclavicular line. His blood pressure ranged from 140 to 145/90 to 92 mm Hg during the examination.

There were no significant abnormalities of the hematologic and biochemical examinations or of the urinalysis.

Chest roentgenograms showed a heart shape consistent with left ventricular hypertrophy, but the cardiothoracic ratio was 41.7 percent and the observed transverse diameter of the heart was 101.4 percent of the predicted diameter for the patient's height and weight.

The resting electrocardiogram showed moderate leftward deviation of the QRS complex and T axis and Q waves in leads II, III and aVF, consistent with an old diaphragmatic myocardial infarction. The voltages in leads I and III and in the precordial leads did not meet the usual criteria for left ventricular hypertrophy but the R wave in lead aVL was 15 mm.

The electrocardiogram was recorded over a 24 hour period during a standardized routine of position, activity, food intake and sleep, using an apical sternal lead with electrodes over the junction of the second rib and the sternum, and over the sixth rib in the nipple line on the left. Throughout the day the patient's heart rate was within the expected range for men of his age under the conditions of this routine, but the rate response to a standard exercise was excessive. Walking on a treadmill at 1.5 miles/hour up a 12 percent grade for 7 minutes produced a maximal heart rate of 145 beats/min (expected rate 110 to 130 beats/min). The record contained 107,120 cardiac complexes, of which 65 were premature complexes of A-V junctional origin and 63 were premature complexes of probable left ventricular origin with coupling intervals that ranged from 370 to 620 msec (Table I, Fig. 1 and 2). Because of the short coupling interval of 22 of these complexes with the R-R′/Q-T ratio between 1.0 and 1.1, they were classified as "early cycle" ventricular premature contractions although none actually encroached upon the T wave. At this time he was receiving Coumadin®, 2.5 mg daily, but no other medication.

Blood pressure was measured frequently while the 24 hour electrocardiogram was being recorded. It was 146–150/90–120 mm Hg when the patient was active and was being interviewed, examined and tested; but in the evening before he went to bed it was 126/76 mm Hg and it was at this level in the morning when he awoke.

Course Under Observation

When he was examined for the second time 1 year later, he stated that he was having episodes of anginal pain more than five times a day. He denied having had prolonged episodes of chest pain or disabling illnesses in the interval, and his employment record indicated no significant absence during this time. However, his electrocardiogram showed a significant loss of amplitude of the R waves in leads V_2 to V_4 with high frequency notching of the S wave in V_2 consistent with the occurrence of an anterior myocardial infarct in the interval. A tape recording obtained as he went about his usual activities over a 24-hour period contained only two premature contractions of ventricular origin, one of which was early cycle and had the same left ventricular configuration as those found in the tape recording of May 1971.

Third and fourth examinations were carried out in February and July 1973. At these he reported that he continued to have anginal pain as frequently as 10 times a day. In July, a 21 hour recording contained 27 ventricular premature contractions in the same form, of which 18 were early cycle. This recording also contained premature ventricular complexes of two other forms (Table I). The transverse diameter of the heart shadow had increased to 16.4 cm (113 percent of predicted value for height and weight).

Findings on Day of Death

At his fifth examination in March 1975, on the morning of his death, he was described as "happy and relaxed, but otherwise no different." On this occasion as on all others he was described as a driving impatient man who minimized the extent of his disability and tried to disregard his symptoms. He reported that he was having anginal pain "about 15 times a day." In response to a questionnaire, he said that he sometimes became short of breath when walking on level ground with people his own age. In January on a skiing trip to a high altitude in Colorado, he had found it difficult to breathe and

TABLE I

Premature Complexes During Four Recordings of the Electrocardiogram

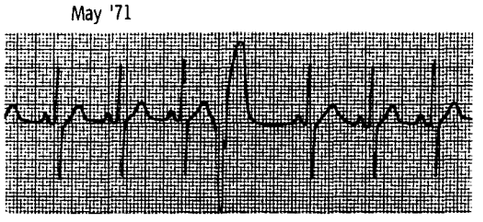
Date	Duration (hr)	Total Complexes	Atrial		A-V Junctional		Ventricular				
			Total	Rate/ 1000	Total	Rate/ 1000	Total	Rate/ 1000	Form I	Form II	Form III
May 1971	24	107,120	1	0.009	65	0.607	63	0.588	63	...	...
April 1972	24	*	5	...	109	...	2	...	1	1	...
July 1973	21	80,460	7	0.087	88	1.094	84	1.044	27	42	15
March 1975	8	41,940	1	0.023	105	2.504	53	1.264	53	...	...

* Accurate count not possible because of artifact.
"Form I" is the "left ventricular" form (see Fig. 3).

had had to sit up most of the night. Shortly after that he had fainted while standing on a crowded train going to work. He recovered immediately after his collapse but rode the rest of the way sitting on the floor. Three days before his death he had been away on another skiing trip but spent most of the weekend indoors because of shortness of breath. He had not seen his private physician for several months although he had repeatedly been advised to do so.

On superficial observation he seemed to be quite well. He had gained 4 kg in 3 months. He was not acutely dyspneic or orthopneic. His lung fields showed no evidence of congestion on X-ray examination. His heart shadow had not increased in diameter since the last film, but was still 113 percent of the predicted value for height and weight. His vital capacity was 87 percent of the predicted value. His blood pressure was 142/90 mm Hg when the examination began but increased to 158/120 mm Hg by the end of the examination. His standard electrocardiogram was unchanged since the last previous examination. Biochemical and hematologic examinations were normal.

After the recorder was attached, the patient went to his office and carried out a usual day's work. His secretary, who had worked with him for many years, noticed "nothing unusual" about him. At a business lunch his associates found him to be cheerful, unconcerned and "his usual self." The diary that he kept throughout the day described no unusual symptoms or activities. During the afternoon he sat at his desk doing paper work, dictating and answering the phone. In mid afternoon his secretary said that he "became upset about a report" from one of his subordinates but she said that this was "not unusual—he frequently became upset about reports that he did not like, but he got over it within a little while." When she left the office shortly before 4:30 PM, she noticed nothing unusual about him. He told her that he intended to remain in the office for a short while to carry out a few last minute chores.



Premature complex, left ventricular form, 'early cycle'
Coupling interval 360 msec
R-R'/QT=1.00
Frequency 0.6/1000 complexes

FIGURE 1. Electrocardiogram, May 1971.

The Terminal Episode

Every day it was his custom to walk from his office to Grand Central Station where he took a train to his home in the suburbs. His diary indicates that he left the office on this day at 5:02 PM. The duration of the walk to the station, as indicated by the diary and by the tape recorder, was 15 minutes. Observers noted that when he sat down on the train he seemed to be unhurried, in no distress, and appeared to have no premonition of impending death. As he sat down, he folded his coat and placed it on the seat beside him, and then made an entry in his diary. This indicated that he had arrived at the train at 5:17 PM, some 15 minutes before it was due to leave. The note was in his usual firm handwriting and made no mention of any symptoms.

About 5:27 PM, a passenger sitting nearby noticed that he had slumped against the window and appeared to be ill. The passenger summoned the conductor, who was on the platform outside and responded immediately. At 5:28 PM, the conductor found the subject to be unconscious and making jerking movements with his arms, but his skin color appeared to be

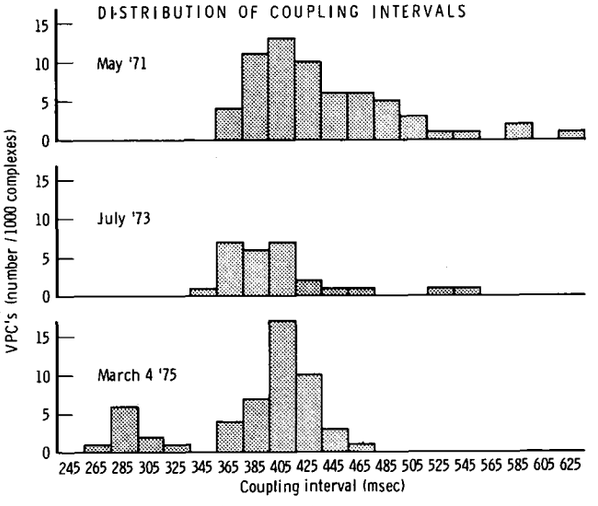


FIGURE 2. Distribution of coupling intervals in three recording periods.

good. The conductor immediately summoned the railroad police, who arrived within 2 minutes with a stretcher. At 5:30 PM, they found the subject to be "grey" and to have no pulse. The jerking movements of his arms had ceased. They carried him to a nearby medical room and administered oxygen. An ambulance arrived within a few minutes. The ambulance crew made efforts at resuscitation but did not attempt defibrillation. When their efforts failed, they pronounced the subject dead at 5:55 PM, 30 minutes after the arrhythmia began. The cardiac recorder was not disturbed until 15 minutes after the subject had been declared dead and 45 minutes after the terminal episode had begun.

Tape Recordings of the Terminal Episode

The tape recording was complete and of excellent quality. It showed that the subject's heart was in sinus rhythm with rates of 70 to 90/min throughout the day, until shortly before death. There were 41,940 cardiac complexes in the 8-hour record, including 105 premature complexes of A-V junctional origin and 53 of ventricular origin, all of which had the same "left ventricular configuration" as those seen in the first record. Forty-three of these ventricular premature contractions occurred before the subject left the office and walked to the station; 22 had short coupling intervals with an R-R'/Q-T ratio of 1.1 or less and were considered "early cycle."

Shortly before the patient left his office a pair of premature ventricular complexes occurred. Both were "early cycle" but neither encroached upon the T wave. During the walk sinus tachycardia (up to 165/min) developed. There were two junctional premature contractions and one ventricular premature contraction during this walk. None of these were "early cycle." Toward the end of the tachycardia there was a distinct depression of the S-T segment. This disappeared promptly as the tachycardia subsided.

Three minutes after the patient sat down in the train, his heart rate had returned to 90/min. Two minutes later a left ventricular premature contraction appeared with a much shorter coupling interval (R-R'/Q-T = 0.89) placing it near the "vulnerable period" of repolarization (Fig. 3A). Ventricular premature contractions with such short coupling intervals had never appeared on any previous recording. One minute later, another such complex appeared. Shortly thereafter there was a pair of premature complexes, of which the first was in the vulnerable period but the second was not. During the succeeding minute he began to have ventricular trigeminy with every third cardiac complex being a premature contraction on the T wave. After five such cycles, the heart returned to a sinus rhythm for a few beats. At 5:25:30 he had a ventricular premature contraction in the vulnerable period, followed by another, also in the vulnerable period. This initiated a ventricular tachycardia that rapidly degenerated into a ventricular flutter at a rate of 300/min, and then into ventricular fibrillation (Fig. 3B).

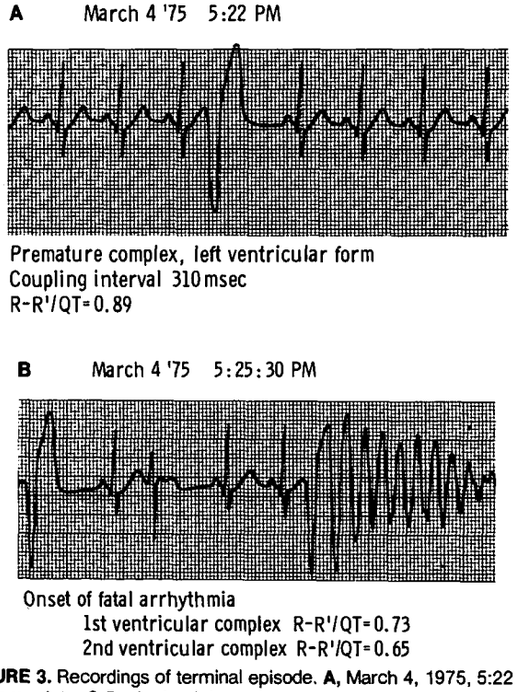


FIGURE 3. Recordings of terminal episode. **A,** March 4, 1975, 5:22 PM; **B,** same date, 3.5 minutes later.

The fatal ventricular fibrillation continued for 23 minutes. During this time the electrical signals gradually degenerated to a straight line consistent with ventricular standstill. Standstill continued for 2 minutes. In the 25th minute he began to have small, isolated but readily identifiable ventricular complexes at a rate of 23/min. These continued for an additional 15 minutes. The last cardiac activity was recorded 40 minutes after the arrhythmia began.

Findings at Postmortem Examination

The heart weighed 628 g. There was massive hypertrophy of the left ventricular myocardium (Fig. 4). The left ventricular wall measured 25 mm, the right 4 mm. There were an old myocardial infarct involving the inferior wall of the left and right ventricles and an old anterior myocardial infarct involving the left ventricular wall. No recent myocardial necrosis was found. Severe atherosclerosis with calcification was present in all major coronary arteries. There was old stenosis of the left anterior descending artery with recanalization, and old proximal stenosis of the left circumflex artery. The lumen of the proximal right coronary artery was partially occluded for a distance of 3 cm by organizing and partially recanalized mural thrombi. Some of these newly formed channels had recently rethrombosed.

Discussion

Although electrocardiograms have been recorded at the time of death of many patients, both within and without the hospital, to our knowledge this is the first case of "unexpected sudden death" that has been studied so intensively in advance and has been observed and recorded so completely at the time of its occurrence. It illustrates many of the features of people who have experienced sudden death due to arrhthymia in random samples of men that we have followed prospectively.[9] In these samples, men who have died from coronary heart disease within a relatively short period (5 years or less) after the last examination have been characterized by a combination of severe myocardial disease and a serious disorder of rhythm or conduction. This has been observed in 80 percent of cases, and it may have been a feature of almost all cases because a number of the men in these samples were examined several years before their death, and there is reason to believe that additional manifestations of heart disease developed after their last examinations.

Before his death, our subject had a scarred ischemic hypertrophied and failing myocardium and he had ex-

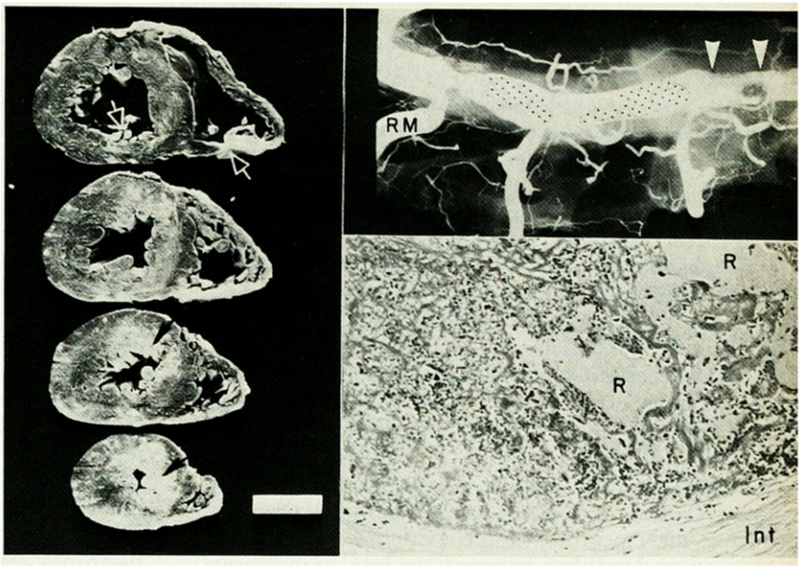


FIGURE 4. Postmortem examination of heart. **Left,** serial slices of the ventricles demonstrating old inferior **(open arrows)** and old anterior **(solid arrows)** myocardial infarcts. There is no evidence of recent necrosis. **Top right,** postmortem coronary arteriogram showing the proximal half of the right coronary artery (blood had flowed from right to left). There is subtotal occlusion of the right coronary artery by a recanalized thrombus **(between arrowheads). Shaded areas** outline additional mural thrombi. There is an old stenotic lesion near the origin of the right marginal branch (RM). **Bottom right,** photomicrograph of recanalized thrombus in the right coronary artery. Some of the newly formed channels (R) are patent; others, toward the left of the picture, show evidence of recent thrombosis. Int = intima. (Hematoxylin-eosin ×120, reduced by 31 percent.)

perienced a recent coronary thrombosis; he also had early cycle ventricular premature contractions. We recently reported[11] results of a 10 year prospective study indicating that the risk of death associated with ventricular premature contractions is greatest when these occur in a setting of serious myocardial disease and the risk is especially great when they occur in the presence of a myocardium that is ischemic, hypertrophied and failing. On the other hand, frequent ventricular premature contractions and even complex ventricular dysrhythmias occurring in the absence of serious myocardial disease have a relatively benign short-term prognosis. Throughout the period of observation, this man had an increasingly ischemic and hypertrophied myocardium and he finally manifested evidence of progressive congestive heart failure. This suggests that his myocardium was becoming increasingly vulnerable to fibrillation during the time when the mean coupling interval of his ventricular premature contractions was becoming progressively shorter.

Early cycle ventricular premature contractions and risk of sudden death: Since the report of Smirk and Palmer[12] in 1960, it has been appreciated that early cycle ventricular premature contractions occurring in the vulnerable period of the cardiac cycle (R-R′/Q-T ratio 0.85 or less) after a recent acute myocardial infarction often precipitate ventricular fibrillation. During acute myocardial infarction, there is also an added risk of death associated with ventricular premature contractions that occur at or near the end of the T wave, apparently because there is an increased probability that additional premature contractions will occur in the vulnerable period.[13,14] In 1971, Moss and his co-workers[15] reported that patients in the recovery period of an acute myocardial infarction also have an increased risk of death if they have early cycle ventricular premature contractions; later they[16] found that such early cycle complexes increased the risk of death over a period of 2 years after infarction. Recently, we[17] reported that early cycle ventricular premature contractions carry an added risk of death even when they occur in ambulatory middle-aged men who have hypertensive or ischemic heart disease but are not acutely ill.[17] The risk is partly independent of the frequency of ventricular premature contractions in the recording.

Our subject had ventricular premature contractions of probable left ventricular origin in his first recording in 1971, some of which occurred early in the cardiac cycle (R-R′/Q-T ratio 1.1 or less). During the next 4 years, their frequency increased slightly. Their mean coupling interval became shorter, and a larger proportion of them were "early cycle"; but none of the recorded ventricular premature contractions encroached on the T wave until 5 minutes before the fatal arrhythmia when they began to appear with shorter and shorter coupling intervals with increased frequency and in pairs. The fatal arrhythmia was initiated when a ventricular premature contraction in the vulnerable period was immediately followed by a second, also in the vulnerable period. The transition from late to early cycle ventricular premature contractions, although searched for in previous studies, was not actually observed and recorded until the present case. It may provide an important link in the understanding of the relation of ventricular premature contractions to sudden death.

Between 1971 and 1975, our subject undoubtedly had many thousands of "early cycle" ventricular premature contractions in which the QRS complex occurred immediately after the T wave. If these contractions occurred at an estimated frequency of approximately 25/day, more than 35,000 would have occurred during this period. One can speculate that the transition to ventricular fibrillation finally occurred when the increasingly vulnerable myocardium was exposed to ventricular premature contractions appearing increasingly early in the cardiac cycle.

Precipitating causes of fatal ventricular fibrillation: Role of exercise: One can also speculate that the electrical phenomena that led to the fatal fibrillation may have been precipitated by two events on the day of death. One event was a new and apparently asymptomatic thrombosis of some of the recanalized mural thrombi in the right coronary artery. This may have produced additional myocardial ischemia associated with a further increase in susceptibility to fibrillation or it may have been a factor in shortening the coupling interval of the ventricular premature contractions. The second event was the walk to the station. This walk was a usual activity for this man and was usually undertaken at a relatively leisurely pace. Because the duration of the walk on the day of death was the same as on other days, our subject apparently did not walk faster than usual on this day. However, the state of his myocardium at this time was such that the walk produced sinus tachycardia (rate 165/min). Toward the end of the walk transient electrocardiographic evidence of ischemia developed, and within 8 minutes, the fatal arrhythmia occurred.

It is well known that electrocardiographic evidence of myocardial ischemia is often more striking after the end of a period of exercise than during exercise, and that it may persist for 10 minutes or more. It is also well known that periods of exercise may be followed by bursts of ventricular premature contractions and more complex dysrhythmias. This may have been a factor in our subject's death. Since 1946 various observers have noted a tendency for sudden death to occur shortly after exercise.[3,18] In our series, 6 of 37 sudden arrhythmia-induced out of hospital deaths occurred a few minutes after the end of a period of activity. This number is greater than one would expect if there were an equal chance that each death might occur at any time during the 24 hours (expected 0.77, observed 6; ($P < 0.001$).*

Clinical features predisposing to sudden death: The "unexpectedness" of this man's death is worthy of mention. He was like many men in our series in that neither his associates nor the physicians who were attending him were aware of the increasing seriousness of his heart disease and the high probability of the early occurrence of a fatal event. In part this can be attributed to features of his personality that were like those that have repeatedly been described among patients with coronary heart disease.[19-21] He disregarded and tried to ignore the symptoms of his disease, and he could not be persuaded to change his pattern of activities in the face of increasing cardiac disability.

There were also features of the illness itself that caused its severity to be underestimated. The patient's blood pressure, which was significantly high during the day when he was active, was borderline or "normal" when it was taken in a physician's office, leading to the impression that he had only "borderline" hypertension. The massive left ventricular hypertrophy that was found at autopsy was not reflected in the early chest roentgenograms and the progressive increase in the transverse diameter of the heart shadow was not remarked upon until the cardiothoracic ratio exceeded 50 percent. The voltage in the bipolar limb leads and in the precordial leads of the electrocardiogram did not meet the usual criteria for a pattern of left ventricular hypertrophy and the significance of the tall R wave in lead aVL was not appreciated. To casual observers, his ischemic heart disease appeared to be relatively asymptomatic. He said little to his associates or his physician about his increasing angina pectoris. The apparent myocardial infarction he experienced in 1973 was not associated with symptoms that he reported at the time or recalled on subsequent questioning, and his company had no record of any acute illness or any period of disability in the interval. The very recent thrombosis of the right coronary artery, which was found at autopsy and which apparently continued to the day of his death, did not cause him to complain of any new symptoms and did not produce changes in appearance or behavior that were remarked upon by his associates. Although the unexplained episode of syncope that occurred about a month before his death should have created a strong suspicion of cardiac dysrhythmia, the standard electrocardiogram provided no indication of the fact that he was having early cycle ventricular premature contractions. These were discovered only with the use of prolonged tape recordings.

* Computation based on the Poisson distribution with $\mu = np = 0.77$. The probability of 6 of 37 deaths occurring within 30 minutes of a period of exercise (under the null hypothesis that risk of death is independent of activity) is $P = 0.00013$. In fact, the probability of observing more than two deaths under this null hypothesis is significant at the 0.05 level ($P = 0.043$).

Acknowledgment

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